REMARKS

By an Office Action dated March 25, 2003 in the file of the above-identified patent application the Examiner rejected the application on a grounds under 35 U.S.C. § 112, as well as on prior art grounds. By amendments to the claims made above, and arguments presented herewith, the applicant has responded to each of those grounds of rejection. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

The Examiner first noted that the applicant failed to comply with the sequence listing requirements since the disk sent to the Patent and Trademark Office was apparently inoperative. A substitute disk is submitted herewith. The undersigned, registered to practice before the U.S. Patent and Trademark Office, states that the contents of this disk and the contents of the sequence listing previous filed in this patent application are identical.

The first rejection in which the Examiner has maintained is under 35 U.S.C. §112, first paragraph, based on the written description requirement. The Examiner acknowledges that the specification discloses a soluble truncated low density lipoprotein receptor and that tagged with an endoplasmic reticulum localizing signal is able to decrease apoB secretion *in vivo* and *in vitro* and thus reduce LDL synthesis. The Examiner objected to the claims because the claims encompassed a genus of LDL receptors that do not include the domain of native protein associated with membrane binding. The Examiner argues that the specification does not teach which parts of the LDL receptor is functional to have such effects and that other fusion proteins made with other truncated LDL receptors might not have the same effect. The Examiner also objected to the recitation of the localization domain on the grounds that it was too broad as well.

Based on these recitations, the applicant has amended the description of the LDL receptor portion of the fusion protein of the present invention and of the localization domain. It is now specifically recited in the claims that the LDL receptor used in the present invention is a truncated form of the receptor which includes the domain providing the function of binding to low density lipoprotein but does not include the domain of the native protein associated with membrane binding or the domain associated with the O-linked sugars. Please note that the state of the art includes teachings of the previously cited U.S. Patent No. 5,521,071, which teaches precisely that the inclusion of the first seven amino terminal imperfect sequence repeats and at least one of the two following imperfect sequence repeats can function alone as a binding domain for low protein lipoprotein. The prior art is generally aware of extensive studies conducted on the low LDL receptor and has exhaustively studied the fact that the LDL binding domain of the native protein is the first 242 amino acids of the

protein. As the specification of U.S. Patent No. 5,521,071 teaches, even part of that ligand binding domain, the second imperfect repeat, can be omitted while still retaining the function of binding to LDL. Accordingly, since the function of this portion of the fusion protein of the present invention is specifically to bind LDL, and the claims specifically recites including the well-characterized domain which has that function in the fusion protein, there is not indefiniteness.

The applicant's written description must be such as to enable one of ordinary skill in the art to practice the breadth of the invention. It is within ambit of ordinary skill the art to identify the LDL binding portion of the LDL receptor protein. The prior patent cited in the specification, U.S. Patent No. 5,521,071, does precisely that. Accordingly, using that language which is neither indefinite nor overbroad.

As to the localization domain, the claim has been amended to recite clearly that the localization domain directs localization of the fusion protein to the endoplasmic reticulum. The applicant has identified seven localization domains which will accomplish this effective and has a teaching in the specification of other modifications to proteins which will have the same effect (specification page 4-5). Accordingly, it is submitted that this recitation of the claims is not overbroad. It is limited to the embodiments of the present invention which have worked, i.e. where the fusion protein is directed to the endoplasmic reticulum. As such, the claims do not violate the written description requirement in our appropriate scope.

Separately, the applicant has admitted a new claim, designate Claim 17, to attempt to overcome this rejection in its entirety.

The Section 112 rejection beginning on the top of page 5 of the Office Action, also under Section 112, first paragraph, is believed addressed as well by the amendments to the claims made above. Again, the fusion protein has been identified with more specificity and that specificity is commensurate with the scope of that which will work.

In this portion of the Office Action, the Examiner searched the breadth of the claims as too broad. The applicants respectfully disagree. Of the specifications now limited to administering the fusion protein with an endoplasmic reticulum localization domain.

The Examiner also questions the fact that the data present in the specification is from the mouse model. The mouse model used in the present specification is a widely accepted model for lipoprotein research. The Examiner has provided no reason why that teaching is not applicable to other mammals. In the absence of a reason as to why the applicants prediction that this technique will work with other mammals, the Examiner cannot reject the applicants claims as lacking in enablement for the breadth of the invention as claimed.

On the top of page 8 of the Office Action is a rejection under Section 112, second paragraph, for wording and formality. The fact that the language of the prior claims could have been read in more than one fashion is well stated by the Examiner. It is believed that the changes made above to the claims have cured that deficiency and made it clear that the fusion protein includes both the truncated LDL receptor and an attached localization domain. It is believed that the amendments above to the claims overcome this rejection.

The Office Action also includes a rejection of the claims under 35 U.S.C. §103. The Examiner argues that Twisk teaches that the level of activity of the LDL receptor is related to the abundance of apoB in an individual. The teaching of the prior Attie patent (5,521,071) is that a soluble LDL receptor including essentially only the LDL binding domain, could still bind LDL effectively. The Examiner argues that combining Twisk with the prior Attie patent makes obvious the use of the truncated LDL receptor to lower aopB levels, and therefore LDL levels, in an individual. The applicants assert that this combination rejection does not make obvious the invention as claimed.

First, the '071 patent discloses that the truncated LDL receptor will bind to LDL. Twisk teaches that the level of LDL receptor is related to the level of apoB in an individual. But neither the '071 patent nor the Twisk paper teaches what portion of the entire LDL receptor protein is responsible for the effect on apoB levels. As can be seen in Fig. 1 of the '071 patent, there is much more to the native LDL receptor protein that in the truncated receptor used in the examples in this application and claimed here. On what basis is it obvious that the truncated form of the LDL receptor would continue to interact with the level of apoB in an individual, as the applicants here have now demonstrated. While this experiment may or may not have been obvious to try, there was insufficient data available to predict the outcome of this work prior to the data disclosed in this patent application.

Secondly, the invention only works when the LDL receptor is localized in the secretory pathway where the apoB is processed. To do this, the LDL receptor had to be localized in the ER. This had not been done before. While the localization domains for the ER were known before, whether or not this level of localization would be sufficient to locate the LDL receptor where it could interact with apoB was unknown. Again, while this approach may or may not have been obvious to try, there was no reasonable expectation of success in this approach. Note that the result in highly specific. Again this could not have been predicted in advance.

In short, the applicants assert that the claimed invention is obvious only in hindsight. The prior art references, taken together, would indicate only that the whole LDL receptor will

lower apoB levels, and that the truncated LDL receptor is soluble and binds LDL. Until the work described here is was non known that the truncated form of the LDL receptor would still react with apoB and have the desired effect or that the attachment of the truncated LDL receptor to the ER would be effective. As such, the invention taken as a while is not obvious in view of the cited prior art.

Based on the foregoing, and early and favorable reply is solicited. A separate petition for extension of time is submitted herewith so that this response is timely filed.

Respectfully submitted,

Nicholas J. Seay
Reg. No. 27,386
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL (608) 251-5000
FAX (608)251-9166